# Statin & New onset Diabetes : Where is the Truth ?

**ATEF ELBAHRY**, FRCPE,FACA,FICA,FISCP

SENIOR CONSULTANT OF CARDIOVASCULAR MEDICINE

VICE PRESIDENT OF EGYPTIAN ASSOCIATION OF VASCULAR BIOLOGY & ATHEROSCLEROSIS




# THE TRUTH & NOTHING BUT THE TRUTH

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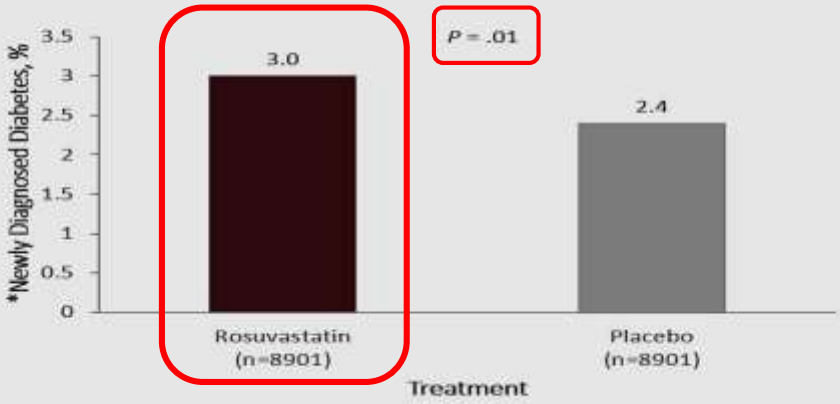
# JUPITER
## *Increased Incidence of T2D With Rosuvastatin*




*Physician-reported diabetes.
Ridker P, et al. *N Engl J Med*. 2008;359:2195-2207.

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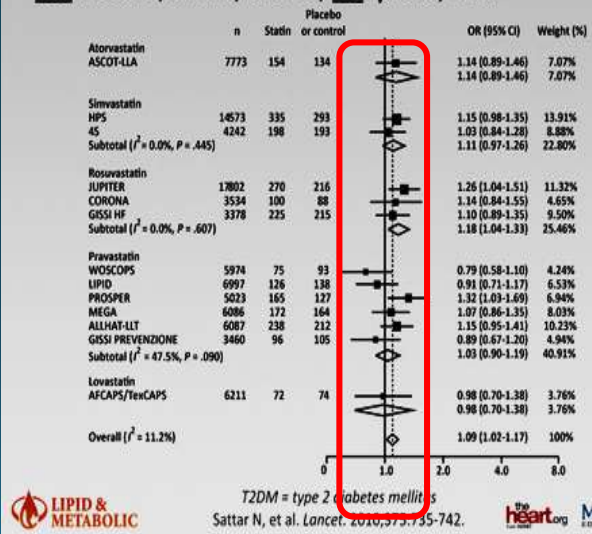
## Certain Statins Increase the Risk of New-Onset T2D

- 13 statin trials
  - 9% risk of diabetes over 4 years (n=91,140)
- Results
  - Statin therapy is associated with a slightly increased risk of developing diabetes
  - Risk is low both in absolute terms and when compared with the reduction in coronary events
  - Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change
  - No risk of diabetes if patient is not pre-diabetic

Sattar N, et al. Lancet 2010;375:735-742.

## Do Statins Increase New-Onset T2DM?
### *Yes*: rosuva, simva, atorva; *No*: prava, lova

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*T2DM = type 2 diabetes mellitus*

Sattar N, et al. *Lancet*. 2010;375:735-742.

the heart.org Medscape EDUCATION

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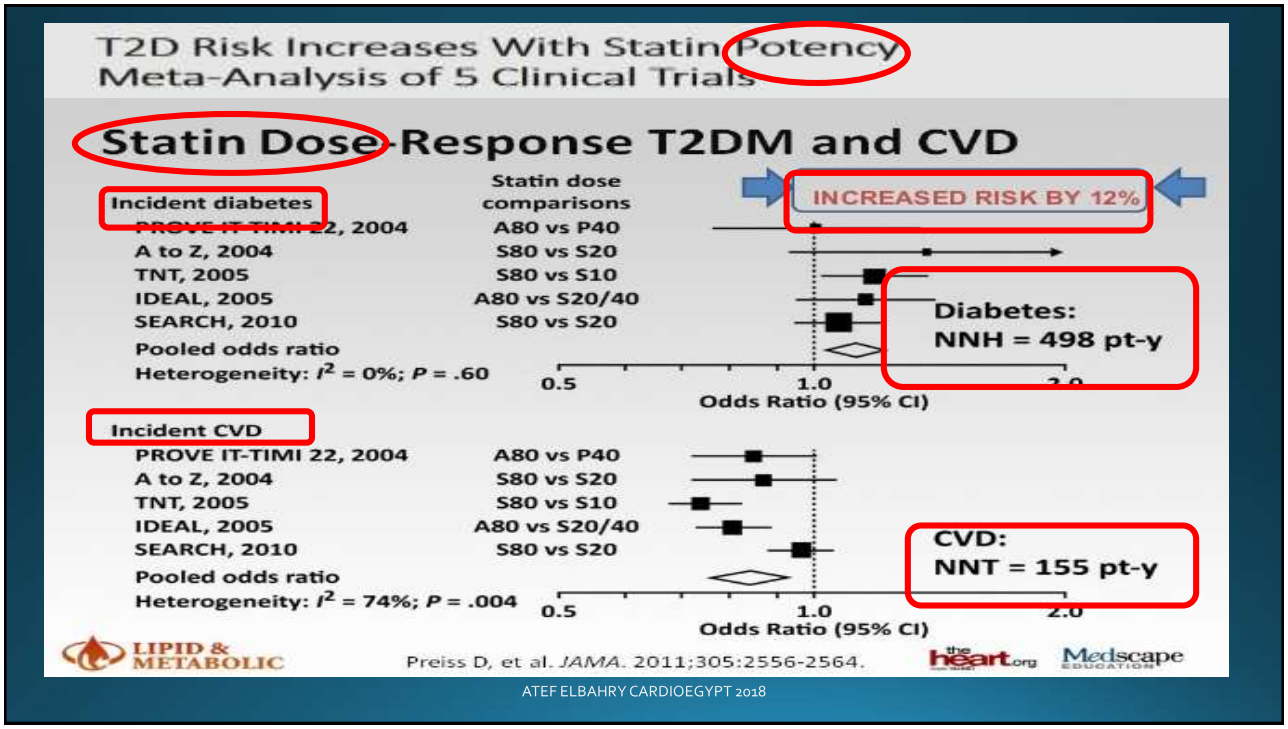
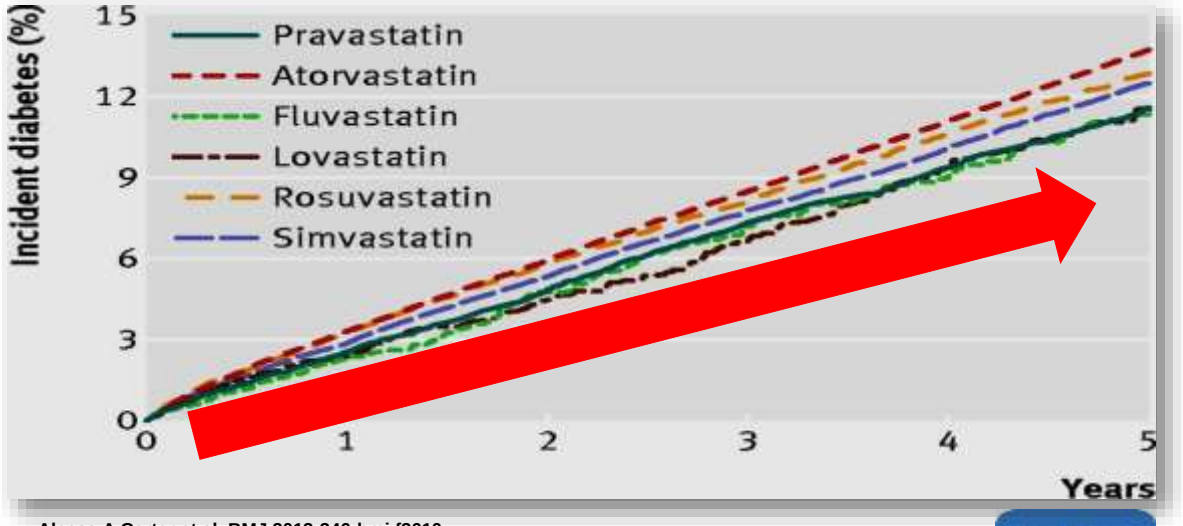



**Adjusted survival curves for incident diabetes among new users of statins.**

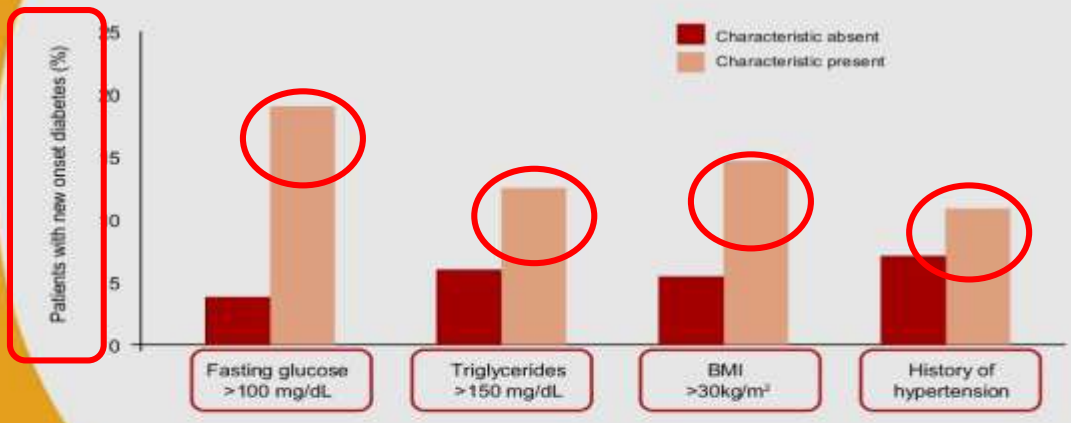



Aleesa A Carter et al. BMJ 2013;346:bmj.f2610

thebmj

## Independent Risk Factors for the Development of Diabetes with High Dose Atorvastatin

**Analysis from TNT* (n=7,595)**




*TNT: Treat to New Targets

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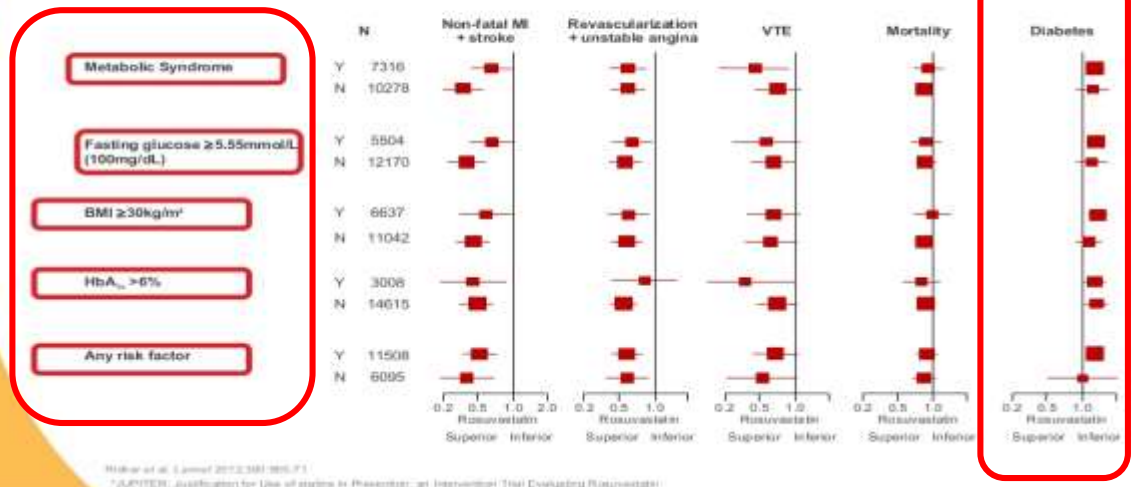
## Risk Factors for the Development of Diabetes in Patients Receiving Rosuvastatin 20mg in the JUPITER* Trial (n=17,603)




*JUPITER: Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

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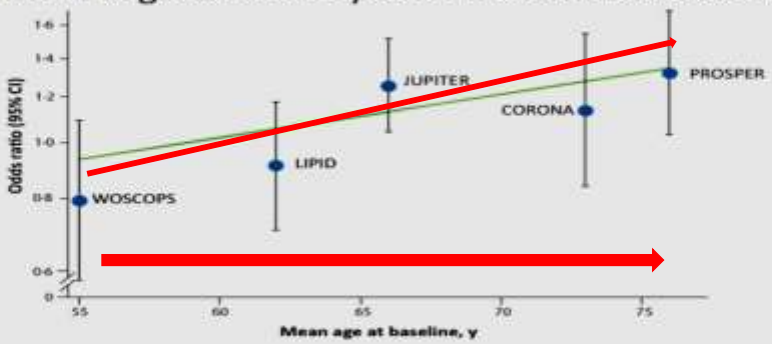
# Risk for New-Onset T2D Stratified by Age

## Meta-Regression Analysis for Incident Diabetes[a,b]




In JUPITER, statin treatment accelerated development of T2D by 5.4 weeks[b]

a. Sattar N, et al. *Lancet*. 2010; 375:735-742; b. Ridker P, et al. *Lancet*. 2012;380:565-571.



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# EFFECT OF HIGH INTENSITY STATINS

## RISK OF INCIDENT DIABETES AMONG PATIENTS TREATED WITH STATINS ± EZETIMIBE: LESSONS FROM A LIPID CLINIC AFTER AN 8-YEAR FOLLOW-UP

F. Barkas[1], E. Rizos[1], E. Liberopoulos[1], E. Klouras[1], Moses Elisaf[1].

[1]Internal Medicine School of Medicine, University of Ioannina, Ioannina, Greece.

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## Results (II)

- During follow-up for an average of 7 years, 12% of the study participants developed diabetes.
- As expected, individuals with prediabetes at baseline exhibited higher rates of incident diabetes compared with those with normal fasting glucose levels (30% vs 4%, p <0.05).

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## Results (III)

In the multivariate regression analysis:

- baseline fasting glucose (beta = 21.68, p <0.01),
- presence of the metabolic syndrome (beta = 1.25, p <0.01),
- family history of diabetes (beta = 1.08),
- duration of follow-up (beta = 1.71, p <0.01),
- and high-intensity statin treatment (beta = 1.35, p = 0.023)

were significantly associated with diabetes development.

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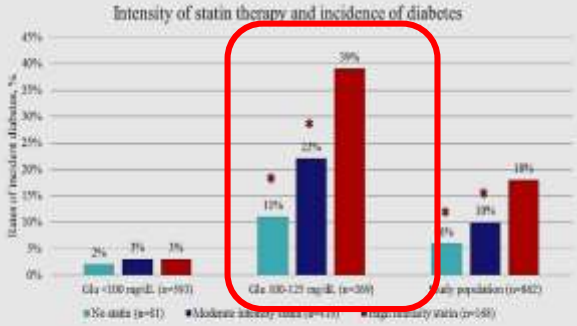
## Results (IV)

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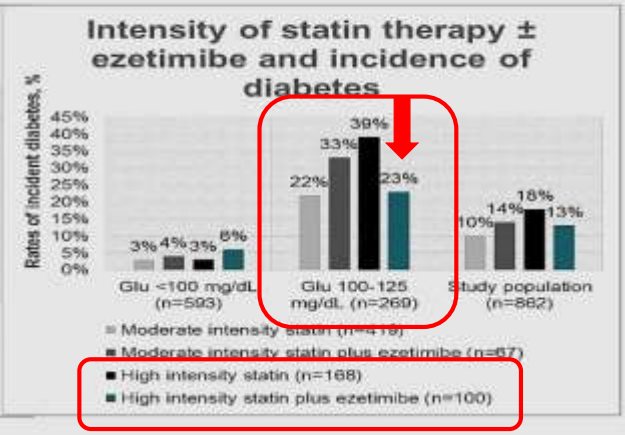
# Results (V)



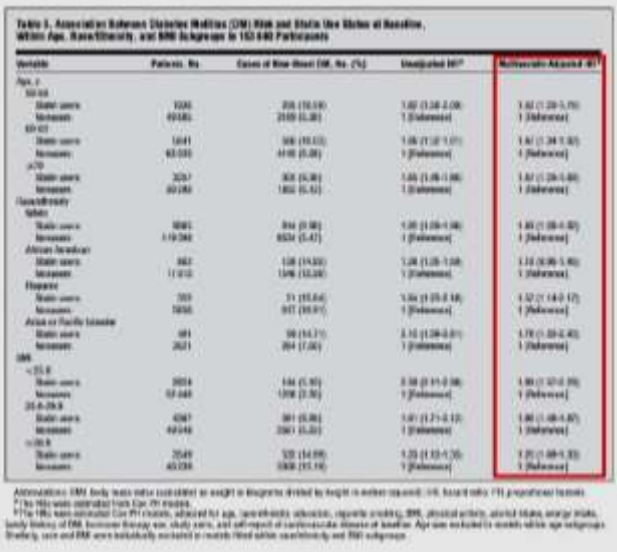

## Outcomes

The increased risk is found throughout all subgroups tested, including:

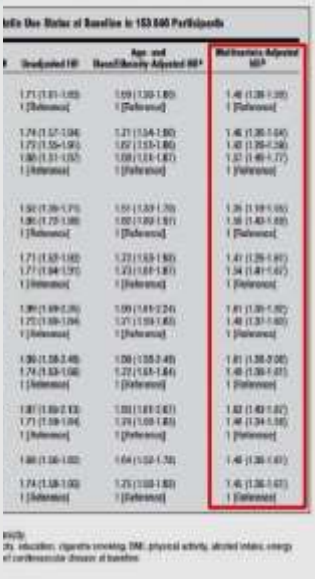
- ✓ Age
- ✓ Race/ethnicity
- ✓ BMI

This holds true even after multivariate adjustment[†]

[†]Except for African Americans, thought this maybe due to a lack of power for this subgroup.



Outcomes



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## Outcomes

A subset of women with and without a history of CVD were analyzed to address the effect of confounding variables and selection bias. There was still a statistically significant increase in incidence DM in the women on statin therapy, regardless of their CVD history (HR 1.46; 95% CI 1.29-1.65).

**Table 4. Risk of Diabetes Mellitus (DM) by Statin Use Among Women With and Without Medical History of Cardiovascular Disease (CVD) at Baseline**

| Description | Women With CVD (n = 24 842) | | Women Without CVD (n = 120 173) | |
|---|---|---|---|---|
| | Statin Users | Nonusers | Statin Users | Nonusers |
| Participants, No. | 3338 | 21 504 | 7089 | 113 084 |
| Incident DM cases, No. | 369 | 1695 | 646 | 6786 |
| Cumulative incidence rate, % | 11.06 | 7.88 | 9.10 | 6.0 |
| Unadjusted HR (95% CI)[a] | 1.52 (1.36-1.71) | 1 [Reference] | 1.69 (1.52-1.70) | 1 [Reference] |
| Age- and race/ethnicity–adjusted HR (95% CI)[b] | 1.52 (1.36-1.70) | 1 [Reference] | 1.61 (1.49-1.75) | 1 [Reference] |
| Multivariate adjusted HR (95% CI)[c] | 1.46 (1.29-1.65) | 1 [Reference] | 1.48 (1.36-1.62) | 1 [Reference] |

Abbreviations: HR, hazard ratio; PH, proportional hazards.
[a] The HRs were estimated from Cox PH models.
[b] The HRs were estimated Cox PH models, adjusted for age and race/ethnicity.
[c] The HRs were estimated from Cox PH models, adjusted for age, race/ethnicity, education, cigarette smoking, body mass index, physical activity, alcohol intake, energy intake, family history of DM, and hormone therapy use.



## How Statins Could Impair Glucose and Insulin Metabolism

**Increased insulin resistance**

- ↓ Adipocyte maturation (immature adipocytes are insulin resistant[a])
- ↓ HMGCR in adipose → ↓ isoprenoids → ↓ GLUT4 → ↓ glucose uptake[b]
- ↓ Adipose SLC2A4 & C/EBPα → ↓ glucose uptake[a]
- ↓ Muscle Akt/FOXO signaling → ↓ glucose uptake[c]

**Decreased insulin secretion and β cell function**

- ↓ GLUT2 in β cells → ↓ glucose uptake → ↓ insulin secretion[d]
- ↓ HMGCR in β cells → ↑ LDL uptake → paradoxical ↑ cholesterol → β cell damage[d]
- ↓ HMGCR in β cells → ↓ ubiquinone → ↓ mitochondrial function → ↓ ATP → ↓ insulin secretion[e]

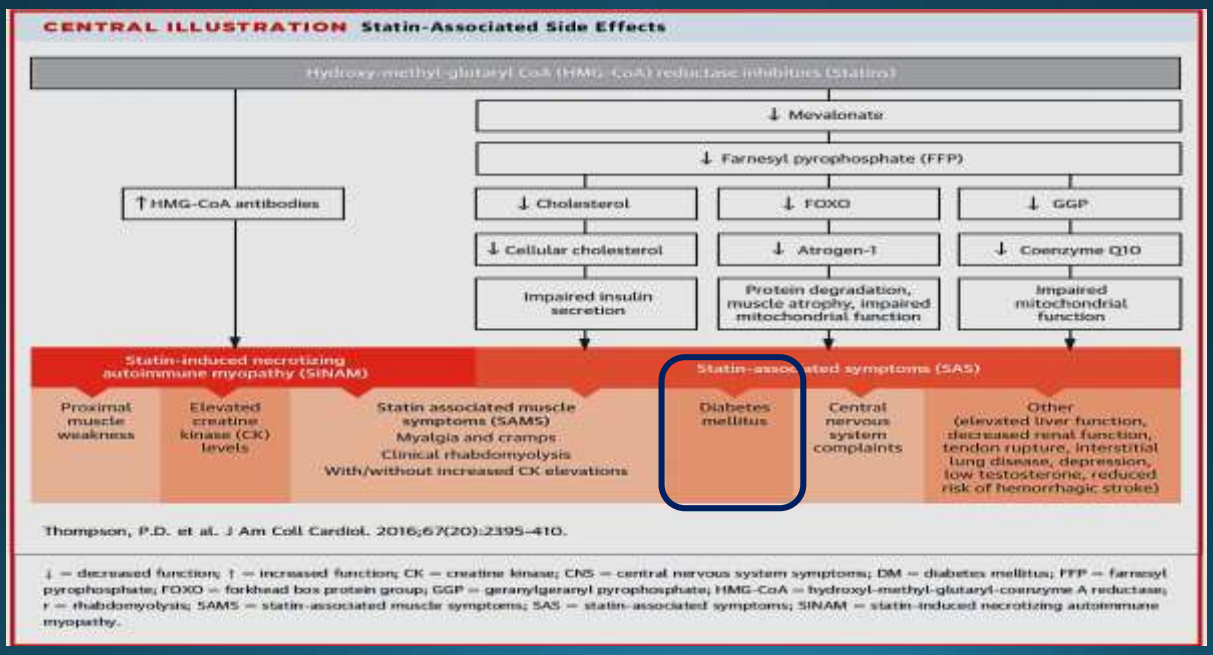
a. Nakata M, et al. *Diabetologia*. 2006;49:1881-1892; b. Baker W, et al. *Diabetes Res Clin Pract*. 2010;87:98-107; c. Mallinson J, et al. *J Physiol*. 2009;587:219-230; d. Kruit J, et al. *Diabetologia*. 2010;53:1110-1119; e. Kruit J, et al. *Curr Opin Lipidol*. 2010;21;178-185.

# Apoptosis of Beta Cells

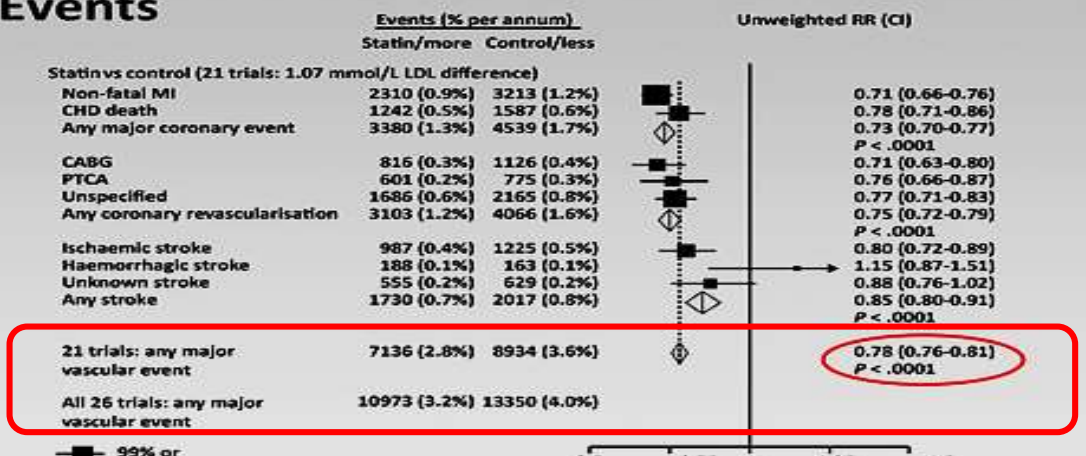
- More cell death in beta cells in vitro exposed to various statins at different concentrations
- Reduced insulin secretion from beta cells exposed to statins impacts insulin response

Qian L, et al. *Med Sci Monit*. 2010;16:HY1-2.





# Impact of Statin Use on Major Vascular Events

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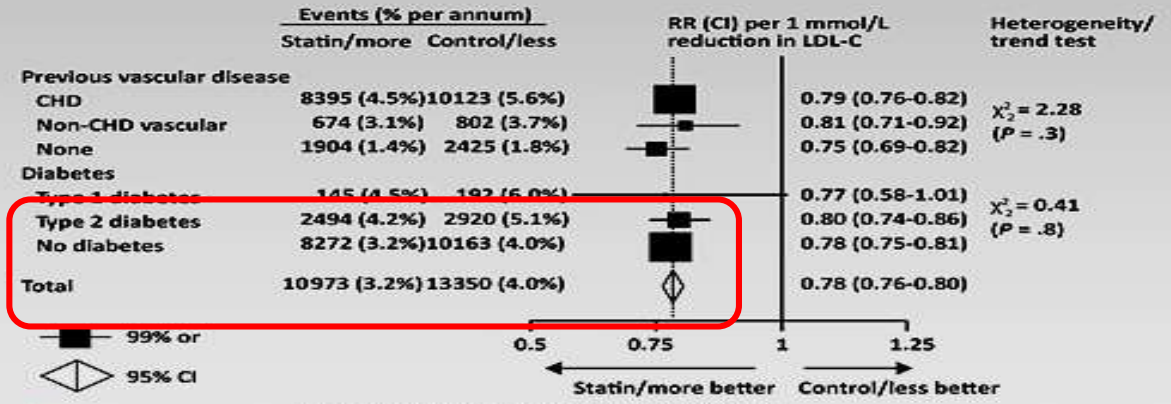
Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2010;376:1670-1681.



# Impact of Statin Use on Major Vascular Events by Baseline Prognostic Factors

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Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2010;376:1670-1681.

# To prescribe or not to prescribe: That is the statin question

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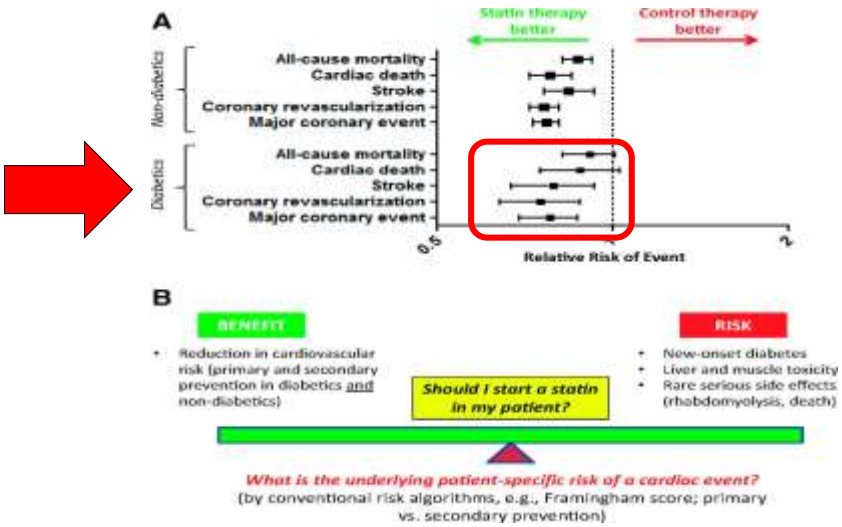
**A, Relative risk of experiencing a cardiac event or death by diabetes status (for a near 40 mg/dL reduction in LDL cholesterol) from a meta-analysis of 14 clinical trials of statin therapy.**




**Ravi V. Shah, and Allison B. Goldfine Circulation. 2012;126:e282-e284**

American Heart Association.

# TAKE AWAY MESSAGE

- YES STATINS INDUCE DIABETES IN PRE-DIABETICS
- THE TRUTH IS QUITE PROVED BY MANY META-ANALYSIS
- BUT

## Statin-Associated T2D Implications for Clinical Care

- Do not discontinue statin
  - Exposes patients to CV risk
- Do not ignore elevated $HbA_{1c}$
  - Manage T2D according to treatment guidelines
- Monitor $HbA_{1c}$
- Counsel patients on lifestyle management
  - Diet, weight, exercise

## Statin Selection Consideration

**Identify patients at risk for new-onset T2D**
- Patients with risk factors for T2D

**In patients with high risk of developing T2D**
- Consider a statin that has a low risk for new-onset T2D

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# THANKS FOR YOUR KIND ATTENTION

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